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Research report

Risk Factors for sleep apnea in children with bipolar disorder

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ABSTRACT

Background: While studies have suggested an increased prevalence of Obstructive Sleep Apnea (OSA) in adults with Bipolar Disorder (BPD), little is published about children with BPD. Behavioral difficulties including emotional liability, depression and poor school performance are commonly reported in children with either BPD or OSA. Comorbid medical disorders may exacerbate the course of BPD. We reviewed demographic and polysomnogram characteristics of children with BPD to help outpatient identification of OSA.

Methods: A single center retrospective chart review of children with BPD referred for a polysomnogram (PSG) over a ten-year period was conducted. There were 27 children identified whose diagnosis of BPD was independently verified by a child psychiatrist using DSM-IV standard criteria.

Results: Six (22%) children had OSA with a median apnea–hyponea index of 7.5 events per hour. Variables that were significantly different between the OSA and non-OSA groups were: median BMI (47 vs 30 kg/m^2, $p=0.001$); sleep efficiency (78.2% vs 91%, $p=0.009$); and oxygen saturation nadir (82% vs 92%, $p=0.0003$). There was no difference found in snoring percentage on PSG between the two groups.

Limitations: The retrospective design from a single tertiary center limited the cohort size. Only secondary verification of the diagnosis of BPD from the available medical record was possible.

Conclusions: Our findings suggest that extreme obesity (BMI >40 kg/m^2), oxygen desaturation during sleep and frequent nocturnal awakenings are associated with OSA in children with BPD. Traditional clinical parameters for obesity and snoring, per se, are poor predictors of OSA in children with BPD.

1. Introduction

Sleep disturbances, such as insomnia, circadian rhythm alteration, and poor sleep quality with daytime sleepiness, are often reported by patients with Bipolar Disorder (BPD) and can be a hallmark of both manic and depressive episodes (Boland and Alloy, 2013). These symptoms frequently persist when these patients are euthymic (Boland and Alloy, 2013; Rocha et al., 2013) and can contribute to baseline depressed cognitive and psychosocial function, which negatively impact treatment efficacy and quality of life (Malhi et al., 2007; Robinson and Ferrier, 2006). But poor sleep quality and daytime sleepiness can also be related to the medications used to treat the disorder.

Obstructive Sleep Apnea (OSA) is a common condition that causes sleep fragmentation resulting from repeated brief upper airway narrowing or closure. In a pediatric population, presenting symptoms of OSA are often different than adults, with symptoms of behavioral or emotional liability, inattentiveness and even hyperactivity being frequently reported (Beebe, 2006; Mitchell and Kelly, 2006; Marcus et al., 2012). The American Academy of Pediatrics reports the prevalence of pediatric OSA between 1.2% and 5.7% of the general population, with pre-school children affected to a greater degree due to their smaller upper airway dimensions. It is widely accepted that OSA affects about 2% for school-aged children (Marcus et al., 2012; Clinical Practice Guideline, 2002). In addition, habitual snoring (defined as ≥ 3 nights per week) is a very common feature of OSA, but often

Abbreviations: BPD, bipolar disorder; OSA, obstructive sleep apnea; PSG, polysomnogram or sleep study; BMI, body mass index; TST, total sleep time

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occurs in children without evidence of OSA (Marcus et al., 2012; Clinical Practice Guideline, 2002; Nieminen et al., 2000).

The overlap of symptoms between BPD and OSA can interfere with appropriate diagnosis and treatment. Both OSA and BPD lead to poor daytime functioning and quality of life indices that can impair treatment efficacy and adherence, exacerbating mood symptoms. Two studies evaluating the prevalence of OSA among adult patients with BPD reported similar rates of nearly 50% (Soreca et al., 2012; Kelly et al., 2013). To our knowledge, there have no reports of the prevalence of OSA among children with BPD. The aims of this study were to assess the prevalence of OSA in children with BPD and determine outpatient clinical parameters that might help identify those with OSA among children with BPD. We hypothesized that snoring, increased BMI and reduced sleep efficiency presenting as insomnia may predict the presence of OSA among children with BPD.

2. Methods

The study was a single center, retrospective chart review of children with the diagnosis of BPD who underwent a polysomnogram for any reason. The study obtained approval from Nationwide Children's Hospital Institutional Review Board prior to chart review and data collection. Nationwide Children's Hospital has an electronic database that contains all polysomnograms performed at this institution and allows queries based on demographic information, medical history, and study data. Children were included in this study if they met the criteria of: (1) the child's polysomnogram was performed at Nationwide Children's Hospital within the past ten years and (2) a diagnosis of Bipolar Disorder was contained within their medical record. To identify records that met our inclusion criteria, a search of the database was conducted using the terms “Bipolar”, “Bipolar Disorder”, and “BPD” with a date limitation of the past ten years. All of the records identified using this search underwent a primary review by the study personnel to confirm a diagnosis of Bipolar Disorder was contained within the medical record of each polysomnogram. In addition, children that underwent multiple polysomnograms within our time frame were identified and only the initial polysomnogram was included in this study.

A secondary review of the identified children was conducted by a child adolescents psychiatrist with expertise in Bipolar Disorder (RK) to confirm the diagnosis of Bipolar Disorder using the DSM-IV standard criteria. Patients were included if there was documentation by a child psychiatrist in their medical record of Bipolar I, II or NOS disorder based on DSM-IV criteria. Children were excluded if a diagnosis of Bipolar Disorder was not able to be confirmed.

Demographic information collected included age at the time of the study, gender, height and weight. Comorbid psychiatric diagnosis and treatment were reviewed by the expert clinician at the time of the secondary review. Medications used for treatment of Bipolar Disorder and sleep disturbance were collected and categorized into five groups: (1) antidepressants, (2) antipsychotic, (3) anti-convulsant, (4) stimulant, and (5) sleep aide medications.

Children were divided into two groups based on the presence or absence of OSA. All studies were scored using the recommended criteria as established by the American Academy of Sleep Medicine (AASM) criteria for pediatric polysomnograms. A hypopnea in children was defined as a 50% decrease in airflow or respiratory effort lasting at least 2 missed breaths from the end of the last normal breathing amplitude association with a 3% or greater oxygen desaturation, or electrographic evidence of arousal, or awakening, or both. An obstructive apnea event was defined as a 90% reduction in airflow lasting at least 2 missed breaths from the end of the last normal breathing amplitude association with sustained or increasing respiratory effort. A clinical cut-off of an objective apnea–hyponea index of 1.5 events per hour or greater was to define the OSA group. Additional data including sleep architectural, arousals from sleep, oxygen saturation nadir, periodic limb movements, and snoring percentage were collected.

The data were analyzed using Microsoft Excel (2010). The descriptive statistics included median and interquartile range for continuous variables and percentages for categorical variables. Mann–Whitney and Chi-square tests were used to compare the groups. A significance value of 5% ($p=0.05$) was used for all tests.

3. Results

There were 263 children identified in the initial polysomnogram electronic database search. After the secondary review, 27 children, or 10% the initial search, met criteria for Bipolar I, II or NOS. There were 17 male and 10 female children with a median age of 13 [3.7 (IQR)] years-old in the study cohort. Of the 27 children in the study cohort, 6 children had OSA producing a prevalence of 22% among the children with confirmed BPD. The median apnea–hypopnea index of OSA group was 7.5 events per hour compared to 0.1 events per hour among the children without OSA. The age and gender difference between the groups was not significantly different. There was a significant difference in the Body Mass Index (BMI) between the group with OSA and the group without OSA at a median BMI of 47 kg/m^2 and 30 kg/m^2, respectively. No child in the OSA group had a BMI below 40 kg/m^2.

Twenty-one children with BPD were found to have a comorbid psychiatric diagnosis including: 14 children with Attention Deficit Hyperactivity Disorder (ADHD), 9 children with Generalized Anxiety Disorder (GAD), 4 children with both ADHD and GAD, 1 child with Obsessive Compulsive Disorder, and 1 child with Post-traumatic Stress Disorder. Twenty-six of the 27 children were taking at least one of the five identified medication classes: 26 (96%) children were taking an antipsychotic medication, 15 (55%) were taking a mood-stabilizing medication, 11 (41%) were taking a stimulant medication, 8 (30%) were taking an antidepressant medication, and 2 (7%) were taking a sleeping aide medication (Table 1). Children in the cohort were treated with an average 3 medications. Three children were treated with a single medication. There were 8 (30%) children that were taking two antipsychotic medications, 3 within the OSA group and 5 within the non-OSA group. The median BMI of the children taking two antipsychotic medications was 34 kg/m^2 and not significantly different from those taking less than two antipsychotic medications.

Among the data obtained from the polysomnograms, three parameters of sleep architecture were found to have a significant difference between the two groups. Total Sleep Time (TST) and sleep efficiency were significantly reduced and stage 1 sleep was increased among children within the OSA group compared to the children without OSA. TST was reduced by 83.5 min with median TSTs of 368.5 and 452 min ($p=0.003$) among children with and without OSA. Sleep efficiency was reduced by 16.8%, with median sleep efficiencies of 74.2% and 91% ($p=0.009$) among children with and without OSA. Stage 1 sleep was increased in children with OSA by 4% of TST with medians of 6% and 2% of TST ($p=0.024$). The difference between sleep stages was not significantly different in terms of percentage of Stage 2, slow wave sleep, or REM sleep (Table 2).

Additional data collected from the polysomnograms revealed a significant difference between the two groups for oxygen saturation nadir, with a median nadir of 82% among child with OSA and a median nadir of 92% among children without OSA. Snoring percentages were not different between the two groups,

Table 1
Patient characteristics of the group with Obstructive Sleep Apnea (6 patients) and the group without Obstructive Sleep Apnea (21 patients).

	OSA Median [IQR]	**No OSA** Median [IQR]
Body Mass Index[a]	47 [4.8]	30 [12.5]
Age	15.1 [3.7]	13.3 [3.9]
	Count (%)	Count (%)
Gender		
Male	3 (50%)	14 (67%)
Female	3 (50%)	7 (33%)
Comorbid diagnosis	3 (50%)	18 (86%)
ADHD	2 (33%)	12 (57%)
GAD	1 (17%)	8 (38%)
ADHD and GAD	0	4 (19%)
Other diagnosis	0	2 (10%)
Treatment medication	5 (96%)	21 (83%)
Stimulant[b]	0	11 (52%)
Antidepressant	2 (33%)	6 (29%)
Antipsychotic	5 (83%)	21 (100%)
Mood-stabilizer	3 (50%)	12 (57%)
Sleep aid	0	2 (10%)

OSA—obstructive sleep apnea, ADHD—Attention Deficit Hyperactive Disorder, GAD—Generalized Anxiety Disorder.

[a] Significant difference between the two groups for BMI ($p=0.001$).
[b] Significant difference between the two groups for proportion treated with stimulant medication ($p=0.03$).

Table 2
Polysomnogram results for the group with Obstructive Sleep Apnea (6 patients) and the group without Obstructive Sleep Apnea (21 patients).

	OSA Median [IQR]	No OSA Median [IQR]
Total Sleep Time (min)[a]	368.5 [61.9]	452 [48]
Stage 1 sleep (%)[b]	6 [2.5]	2 [4]
Stage 2 sleep (%)	60 [12.25]	56 [9]
Slow wave sleep (%)	20 [3.75]	27 [14]
REM (%)	15 [8.9]	15.3 [5]
Sleep efficiency (%)[c]	74.2 [17.1]	91 [11]
WASO (min)	62.5 [42.8]	28 [39]
AHI[d]	7.5 [2.5]	0.1 [0.3]
REM AHI	30 [7.3]	0 [1]
Oxygen saturation nadir (%)[e]	82 [6.3]	92 [3]
Snore percentage (%)	90 [41.2]	10 [70]

OSA—obstructive sleep apnea, REM—Rapid Eye Movement Sleep, WASO—Wake after sleep onset, AHI—apnea–hyponea index.

[a] Significant difference between the two groups for Total Sleep Time ($p=0.003$).
[b] Significant difference between the two groups for N1 sleep ($p=0.025$).
[c] Significant difference between the two groups for sleep efficiency ($p=0.009$).
[d] Significant difference between the two groups for AHI ($p=0.0004$).
[e] Significant difference between the two groups for oxygen saturation nadir ($p=0.0003$).

nor were the number of awakenings and periodic limb movements (Table 2).

4. Discussion

An increased prevalence of OSA among patients with psychiatric conditions has been reported, although most of the information is derived from adult population screening (Alam et al., 2012; Lin and Winkelman, 2012). As mentioned, two studies of adults with BPD reported a prevalence of OSA of nearly half of their patient population (Soreca et al., 2012; Kelly et al., 2013), which is three to four times greater than the prevalence of the adult general population (Peppard et al., 2013). These studies established prevalence based on anthropomorphic information and validated questionnaires. In this study, the prevalence of OSA among children with BPD was 22% and is also much higher than the reported prevalence observed in the general pediatric population. All children in this study were independently confirmed to have BPD and a diagnosis of OSA was established with an attended polysomnogram.

Childhood obesity, defined by a BMI greater than the 95th percentile for age, was a common clinical characteristic between these two disorders. Tonsillar enlargement and obesity are the leading factors for OSA in the pediatric population (Marcus et al., 2012). A common side effect of the medications typically used to treat BPD is weight gain and has been widely reported among children treated for BPD. The median BMI for the study cohort was elevated at 32.4 kg/m^2 with a significant difference between those children with OSA (47 kg/m^2) vs those without (30 kg/m^2). The BMI cut-off for obesity based on the median age of 13 years for the study cohort would be 25.2 kg/m^2 in boys and 26.2 kg/m^2 for girls. Thus, the BMI values for children in both groups would represent significant obesity. Of note, no child in the OSA group had a BMI less than 40 kg/m^2 and only 3 (14%) children in the non-OSA group had a BMI greater than 40 kg/m^2.

Polypharmacy and, in particular, antipsychotic medications as a class have been found to have the most significant potential for weight gain (Reeves et al., 2013; Maayan and Correll, 2011). The odds ratio for obesity among patients treated with antipsychotic polypharmacy was report at 2.28 in one study (Maayan and Correll, 2011). Nearly all of the children in our study were treated with an antipsychotic medication and about half were treated with an anticonvulsant medication. There was no significant difference in the medication class utilization among the two groups, except for a greater use of stimulant medications with non-OSA children. Also, the number of medications used to treat each child was similar between the two groups. Of the 8 children that were taking two antipsychotic medications, the median BMI was 34 kg/m^2 and not significantly different from those taking less than two antipsychotic medications. This leads to the conclusion that extreme obesity is a risk factor for OSA among our study cohort, but not necessarily related to the type of medication used to treat their BPD. This is important as the prevalence of obesity among school-aged children and adolescences has tripled since 1980 (Ogden et al., 2010). Treating obese children with medications that can cause additional weight gain can have further downstream consequences related to weight. Obesity has an important effect on the treatment pediatric OSA as it has been found that a standard initial treatment with adenotonsillectomy may not sufficiently treat OSA in children with co-morbid obesity (Bhattacharjee et al., 2010; Costa and Mitchell, 2009). Structured weight loss programs are an important aspect of care within these patient populations.

There were several aspects of sleep on the polysomnogram that were found to be significantly different between the two groups, including Total Sleep Time (TST), sleep efficiency, Stage 1 sleep, and oxygen saturation nadir. TST was reduced by greater than one hour and sleep efficiency was reduced below the normal cut-off in children of 80%. Increased lighter stage sleep also contributes to poor sleep quality and is collated to the sleep fragmentation from repeated arousals. These finding reflect the common complaint of insomnia seen in pediatric OSA. The other stages of sleep were similar between the two groups, including REM stage sleep when OSA is generally worst. Body position during sleep stages was not accounted for and may contribute the lack of difference between the groups. Oxygen desaturations typically occur with OSA events

and a difference in oxygen saturation nadir between the groups was expected. The degree of separation between the median nadirs (82% vs 92%) was interesting and should warrant further prospective investigation. Overnight pulse oximetry as a single physiologic parameter has not been validated for diagnosis of OSA however.

The percentage of snoring during the polysomnogram was not significantly different between the two groups. This was due to a wide range of snoring percentages in each group. Snoring is often associated with OSA, but it is not specific to OSA. The American Academy of Pediatrics reported prevalence of primary snoring at 12% among pre-school children while the prevalence of OSA among pre-school children is much less.

There is little data regarding the effect on BPD management with the treatment of co-morbid OSA. Identification of children with BPD that have OSA may be important for treatment of both conditions. Improvement in neurocognitive and psychosocial functioning is seen among children treated for their underlying OSA (Marcus et al., 2013). Sleep deprivation and disruption can induce manic episodes and thus improving sleep quality may play an important role in treatment. However, there have been case reports of continuous positive airway pressure (CPAP) inducing mania in adults with BPD (Bergé et al., 2008). Depressive symptoms are commonly reported among children with OSA. A recent metanalysis revealed a modest improvement in depressive symptoms reported after treatment of pediatric OSA with adenotonsillectomy (Yilmaz et al., 2013). In adults, treatment of OSA with CPAP has helped with management in Major Depression, Anxiety Disorder, and Panic Disorder, although CPAP adherence is poor (Lin and Winkelman, 2012).

Pediatric sleep apnea can be a difficult condition to diagnose in an outpatient setting as typical symptoms are often vague and different than adults. Children with OSA often display emotional liability, attention difficulty, and poor school performance, rather than the complaint of daytime sleepiness. This is also true for many other pediatric conditions and can complicate the recognition of completing medical issues. Furthermore, overnight polysomnography is expensive and may not be readily available to primary care or psychiatric providers. The goals of this study were to assess the prevalence of OSA in children with BPD and recognize clinical parameters that could be utilized in an outpatient setting to help identify those with OSA among children with BPD. Our results indicate a prevalence of OSA at 22% compared to the general pediatric population that resides at 2% of school-aged children. Our results also suggest extreme obesity (BMI >40 kg/m^2), oxygen desaturation during sleep and frequent nocturnal awakenings are associated with OSA among children with BPD. Obesity, defined by the traditional clinical boundaries, and the presence of snoring are poor predictors for OSA. There was a significant difference in the oxygen saturation nadir during sleep between the two groups. While there is potential utility for the selective screening with at-home nocturnal pulse oximetry further investigation will be needed to validate this approach. Prospective clinical trials for alternative screening techniques and adherence to treatment programs are warranted given the high prevalence of OSA in children with BPD. Pediatric patients with BPD who are very overweight (BMI >40 kg/m^2) and who complain of poor sleep should be referred for a sleep study to rule out obstructive sleep apnea.

5. Limitations

This study has several limitations. The study cohort was not a cross-sectional community sample of children with BPD, but was selected from a single pediatric tertiary care center, which can limit generalizability due to center-specific biases. Furthermore, the retrospective nature of the study restricted the cohort to only children with BPD in the community that their primary provider felt a polysomnogram was necessary as part of their care. This may lead to a sampling bias of the study cohort.

The respective design allowed for only secondary verification of the diagnosis of BPD, which was dependent on adequate documentation within the patient record. All children in this study had both diagnoses of BPD and OSA evaluated by "gold standard" criteria using all available clinical information, DSM-IV criteria and attended polysomnography. Although this improved the accuracy of each diagnosis, it limited the study cohort to a small number. Potentially some children, who would have otherwise met criteria for entry into the study cohort, were excluded due to loss of data or incomplete data entry into the medical record.

The increased prevalence of OSA in children with BPD reported here is consistent with the findings of OSA in adults BPD cohorts as well as studies indicating an increase prevalence of OSA among patients with other affective disorders (Kelly et al., 2013; Alam et al., 2012; Lin and Winkelman, 2012). This study also highlights important clinical parameters for identifying OSA in children with BPD. The results of this study would ideally be verified in a large multicenter prospective study of sleep in children diagnosed with BPD.

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Conflict of interest
None.

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